FDA's Drug Approval Process: Up to the Challenge?
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Testimony

Introduction

My name is David Fassler. I am a child and adolescent psychiatrist practicing in Burlington, Vermont and a Clinical Associate Professor of Psychiatry at the University of Vermont. On behalf of the American Academy of Child and Adolescent Psychiatry (AACAP) and the American Psychiatric Association (APA), I appreciate the opportunity to submit this testimony regarding the Food and Drug Administration (FDA) approval process.

The AACAP is a medical membership association established by child and adolescent psychiatrists in 1953. With over 7,000 members, the AACAP is the leading national medical association dedicated to treating and improving the quality of life for the estimated 7 - 12 million American youth under 18 years of age who are affected by emotional, behavioral, developmental and mental disorders. The AACAP supports research, continuing medical education and access to quality care. Child and adolescent psychiatrists are the medical specialists trained in the treatment of mental illnesses in children and adolescents.

APA is the nation's oldest medical specialty society, founded in 1844, with over 35,000 members nationwide specializing in the diagnosis, treatment and prevention of mental illnesses including substance abuse disorders.

The AACAP and APA would like to thank Senator Enzi (R-WY), chair of the Health, Education, Labor and Pensions Committee, for holding this hearing and for his interest in the Food and Drug Administration's (FDA) approval process and its impact on pediatric medications used to treat depression.

The FDA's drug approval process is basically sound. However, based on our recent experience with the review of the safety and efficacy of the selective serotonin reuptake inhibitor (SSRI) antidepressants, we believe the process can be further strengthened by implementing four recommendations. First, enhanced reporting of and access to data from clinical trials, including negative trials and unpublished results, in a centralized, publicly accessible registry. Second, an expanded emphasis on post-marketing surveillance and increased funding for long term follow up. Third, the creation of an FDA advisory board focusing on the child and adolescent central nervous system, and fourth, strengthening the workforce of researchers, including experts in pediatric psychiatry and neurology, who can assist with the design, oversight, interpretation and reporting of

clinical research.

1. APA and AACAP Urge Access to Comprehensive Clinical Trial Data

The FDA's mission is to advance public health by helping speed innovations that make medications more effective, safer and more affordable; and to provide physicians and the public with the accurate, science-based information they need to use medications to improve their health. That mission depends on open access to all relevant information from clinical studies, especially those that involve children.

The recent discussion of SSRIs brought to light the fact that the physicians, researchers and the public often do not have access to such full data sets. For example, of the fifteen studies on the use of SSRI's in the treatment of childhood and adolescent depression, only four had been published as of February 2004.

Research is key to understanding the cause of depression, especially in children and adolescents, and access to both negative and positive research findings is essential to help clinicians develop the most effective treatment plans. It is this principle that led the AACAP and the APA, last summer, to urge the American Medical Association, to join their call for the development of a national registry of clinical trials. While the AACAP and the APA are primarily concerned with psychiatric medications, we recognize that a registry will impact all of medicine. Moreover, we also recognize that there is a bias toward the publication of positive research findings, which affects all areas of health care. Physicians and patients must have all available knowledge about a medication's safety and effectiveness before they can make informed decisions about treatment options.

The AACAP and the APA encourage the FDA to provide broader dissemination of information gained from pediatric clinical trials. Label information and package inserts provide critical information to physicians, but we would urge the agency to routinely include any and all data specifically addressing the safety and efficacy of agents when used in the treatment of pediatric patients.

Our organizations want the public and physicians to get the most accurate and up-to-date information about SSRIs and about all psychotropic medication for children and adolescents. For this reason, the AACAP and APA have recently released two guides on the use of medication in treating childhood and adolescent depression - one for patients and families and one for physicians. Both documents were endorsed by numerous medical, family, and patient advocacy organizations. A new web site was launched (www.ParentsMedGuide.org) to share these documents with the public. Material from the website is appended to this testimony. The parents guide provides advice for parents to help them make the best decision for their child or adolescent with depression. It describes what a black box warning means, what prompted the warning on SSRIs, what treatments are most effective in treating depression, and the risks associated with not treating this condition. The physician's guide, while similar to the parent's guide, includes more specific clinical and research data on diagnosis, treatment efficacy, and suicidality in children and adolescents.

a. Prevalence of Depression in Children and Adolescents

Mental and behavioral disorders affect an estimated 20 percent of children and adolescents, or approximately 10 million young people. Tragically, only one in five receive any form of treatment for these disorders (U.S. Surgeon General Report).

Within this total, clinical depression is a frequently occurring disorder. It is estimated that depression affects 2.5% of children and over 8% of U.S. adolescents. These rates account for approximately 2.6 million youth ages 6 - 17 (Birmaher et al).

Depression and related mood disorders are serious illnesses for most children and adolescents diagnosed with the condition. Depression can interrupt a youth's normal emotional development, negatively affect self-esteem, interfere with learning in school, and undermine friendships with peers. Over 500,000 adolescents attempt suicide each year and depression is most often the cause (Kochanek, KD et al).

No single cause of depression has been identified. However, we know that depression is an illness with a pronounced biological basis. Research has clearly demonstrated that depression is associated with deficiencies in specific brain chemicals such as serotonin and norepinephrine. The genes that a child inherits also predispose a person to the illness, but this predisposition, or vulnerability, to depression typically is "triggered" by life events. Researchers have begun to identify these triggers, called risk factors, for depression.

A child's risk for becoming depressed may increase with stress or with an experience of devastating loss or trauma. Behavioral problems and other psychiatric disorders – for example, conduct, attention-deficit, learning, anxiety, and substance abuse disorders -- frequently co-occur with depression and may help explain its onset. A family history of depression or bipolar disorder is also a significant risk factor for depression in a child or young adult.

Because of the severity of the disorder, the AACAP and the APA support treatments that have been shown to be effective in reducing the symptoms of depression and promoting normal development.

b. Antidepressant Medications as Part of Effective Treatment

Medication, specifically antidepressants, can be helpful and even lifesaving for some children who have complex psychiatric disorders such as depression. Medication is most effective when it is used as part of a comprehensive treatment plan, individualized to the needs of the child and family. All children and adolescents who are taking antidepressant medication should be monitored closely by a physician, especially early in the course of treatment, or when medications are being changed or dosages adjusted.

Findings from the NIMH-supported Treatment of Adolescents with Depression Study

(TADS) show that a combination of medication and therapy, specifically, Cognitive Behavioral Therapy, or CBT, are more effective than either option used alone. Family therapy and/or work with the child's school may also be appropriate components of a treatment plan. All interventions have potential risks and benefits, and parents need and deserve access to as much information as possible in order to make fully informed decisions regarding treatment options.
It is important to remember that the majority of children and adolescents with depression who are not identified and treated are likely to have ongoing problems in school, at home and with their friends. Research indicates that more than half will eventually attempt suicide, and an estimated 2- to 5-percent will ultimately die as a result (Formbonne, E., et al).

At the end of this testimony is an overview from ParentsMedGuide.org of depression treatment effectiveness, design of clinical trials and data reporting which sheds additional light on reports of suicidal thoughts by depressed adolescents.

c. SSRIs, Suicidal thoughts and FDA post-market actions

Many psychiatrists, patients and families have found the SSRI antidepressants to be extremely helpful for children and adolescents with depression when they are used in a well-monitored treatment program. In addition, the current evidence does not suggest that these medications increase the risk of suicide. It warrants emphasis that in the data from the clinical trials that the FDA analyzed, which involved more than 4,400 youth with depression, there were no actual suicides.

It does appear that these medications may increase the likelihood that a patient will actually tell someone about their suicidal thoughts or even about a suicide attempt. From my perspective, as a child and adolescent psychiatrist, this is actually a good thing, because it means you have the opportunity to intervene and to keep the person safe. I believe this is why none of the studies have demonstrated any increase in actual deaths from suicide in conjunction with the use of these medications. On the contrary, the adolescent suicide rate in the country has actually declined by over 25% since the early 1990's, in a manner consistent with the increased use of SSRI antidepressants.

We are concerned that the available research findings do not support a warning that may be misinterpreted by some practitioners or parents to mean that antidepressant medications actually cause children and adolescents to commit suicide. Such a conclusion is simply not supported by the data.

The AACAP and the APA supported both the FDA's evaluation of the safety data found in clinical trials of SSRIs and the Columbia University reclassification project, and we continue to support the public discussion of the resulting analyses. We also agreed with the FDA's decision to insert warning language with all antidepressant medications to

alert physicians and families to the need to monitor for signs of new suicidal thinking or activity during treatment, although we feel that the specific nature and frequency of such monitoring should be based on the clinical needs of the child.

Both AACAP and APA did not, however, agree with the action ultimately taken by FDA in October of 2004, to require a “black box warning” on all antidepressant medications prescribed for children and adolescents. We were concerned – and recent data substantiates our concern (such as Medco Health Systems data which indicates that from 2003 to 2004, there was a significant decrease in the rate of SSRI prescriptions for children and adolescents) (Fields)
that such a warning might inadvertently create a greater risk by discouraging families from seeking treatment and by dissuading physicians from the appropriate prescribing of these medications.

We are pleased that the FDA recently modified, with scientific input, the specific language used in the warning to more accurately reflect the actual research findings. The FDA decided to remove language that maintained that a causal relationship between medications and increased suicidality had been established. It also is significant that FDA added the language "in clinical trials" when discussing the findings on suicidal thinking and behavior. In doing so, they are acknowledging the challenges and complexities associated with the translation of research finding into clinical practice. We hope the FDA will be willing to consider further modifications to labeling, package inserts and medication guides as more data becomes available.

2. Further Post-Market Research Needed

The AACAP and the APA call for new research on SSRIs to ensure that these medications are used in the safest and most effective manner possible. We support research efforts now underway, such as the NIMH Treatment of Adolescent Suicide Attempters (TASA) study and the NIMH supported Child and Adolescent Psychiatry Trials Network, a large simple trials network.

The recently reauthorized Best Pharmaceuticals for Children Act (P.L. 107-109) and the Pediatric Research Equity Act (P.L. 108-155), which codifies the 1998 Pediatric Rule, will ensure that pediatric clinical trials will be included during the development of new therapeutic medications, providing child and adolescent psychiatrists with additional safety and efficacy information about new medications. We also suggest Congress consider the creation of an independent body to oversee and advise the FDA on post-marketing issues.

3. Create a Central Nervous System Pediatric Advisory Committee

To provide the FDA with critical expertise on pediatric psychopharmacology, the AACAP and APA support the creation of a Central Nervous System Pediatric Advisory Committee that would be composed of child and adolescent psychiatrists, pediatric neurologists and other experts. This committee would work to improve the quality of life

for the millions of children and adolescents with mental illness and their families.

We are pleased that the Pediatric Research Equity Act strengthened the FDA pediatric research efforts by creating a Pediatric Advisory Committee. While this committee will represent general pediatric research issues, the FDA also requires specialized guidance in pediatric psychopharmacology from experts in child and adolescent mental health and neurology. Pediatricians are not specifically trained in child and adolescent psychiatry or child neurology, and we should not expect general pediatric experts to be able to provide the FDA with the highly specialized expertise in child and adolescent mental illnesses required in pediatric psychopharmacology.

4. Workforce and Access Issues

Family practitioners are more likely than either pediatricians or psychiatrists to prescribe stimulants and less likely to use diagnostic services, provide mental health counseling, or provide follow-up care (U.S. Surgeon General Report). This is also true for antidepressants. Child and adolescent psychiatrists are the only medical specialty fully trained in the diagnosis and treatment of children's mental illnesses, yet there are only approximately 7,500 of these specialists in the U.S. We encourage committee members to support the enactment of the Child Health Care Crisis Relief Act sponsored by Senator Jeff Bingaman.

These bills will help remove one of the main barriers to appropriate treatment for children and adolescents with emotional and behavioral disorders through the creation of educational incentives and federal support for children's mental health training programs. It will authorize scholarships, loan repayment programs, training grants, and specialty training program support. Children's mental health professionals covered under the bill include: child and adolescent psychiatrists, child psychologists, school psychologists, school social workers, school counselors, psychiatric nurses, social workers, marriage and family therapists and professional counselors.

In addition, access to appropriate mental health treatment for children and adolescents requires the elimination of discriminatory policies and practices with respect to health insurance coverage. For this reason, both the APA and the AACAP fully support the passage of parity legislation at both the state and federal levels.

Summary of Recommendations

The AACAP and the APA make the following recommendations:
• Enhance the release and dissemination of data from clinical trials through the development of a centralized, publicly-accessible, national registry.

• Strengthen post-market surveillance and reporting, and provide funding for more short-term and long-term pediatric clinical trials, including follow-up studies, on all medications prescribed for children and adolescents.

• Create an FDA Central Nervous System (CNS) Pediatric Advisory Committee composed of child and adolescent psychiatrists and child neurologists to provide FDA will expertise on pediatric psychopharmacology. Also consider the creation of an independent body to oversee and advise the FDA on post-marketing issues.

• Pass legislation to increase the numbers of children's mental health specialists available to study and treat disorders such as childhood and adolescent depression, including the "Child Healthcare Crisis Relief Act" sponsored by Senator Bingaman, and the "Children's Compassionate Care Act of 2005" S. 174 sponsored by Senators DeWine, Dodd and Murray.

Conclusion
The AACAP and APA appreciate this opportunity to submit testimony on the FDA's approval process as it relates to pediatric antidepressants. Both organizations are eager to work with Members of Congress to address the issues related to research into childhood mental illnesses and the training, treatment and services needed to assure that children with psychiatric disorders receive the appropriate and effective intervention that they need and deserve.

Endnotes from written testimony:
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U.S. Department of Health and Human Services. Mental Health: A Report of the Surgeon General. Rockville, MD: U.S. Department of Health and Human services, Substance Abuse and Mental Health Services Administration, Center for Mental Health Services, National Institutes of Health, National Institute of Mental Health, 1999.

From the ParentsMedGuide.org

Overview of treatment effectiveness and suicidality
The effectiveness of treatment was demonstrated recently in a definitive study supported by the National Institute of Mental Health (NIMH). The Treatment of Adolescents with Depression Study (TADS) (March, J et al) showed that a combination of fluoxetine (Prozac®) and cognitive behavior therapy (CBT) led to significant clinical improvement in 71% of moderately to severely depressed adolescent patients. Improvement rates for other treatment groups in the study were 61% for fluoxetine alone, 43% for CBT alone,

and 35% for placebo. This finding replicated two previous positive studies in pediatric populations (Emselie GJ, Rush, et al), (Emslie GJ, Heilgenstein JH, et al).

A key finding of the TADS concerned the positive impact of treatment on suicidal thoughts and behaviors, or "suicidality," in depressed youngsters. Suicidal ideation is a key symptom of major depression. It is typically present before the start of antidepressant treatment and is one of the major symptoms targeted for treatment. Since mood disturbances often are among the last symptoms to remit in treatment, and because antidepressant medications typically require several weeks to exert a clinical effect, the initial changes in brain functioning brought about by treatment are often not adequate to suppress suicidal thoughts. In the event that worsening might occur, the physician, in collaboration with the child's parents or other family members, must appreciate the importance of intensively monitoring a pediatric patient to assure patient safety during the early stage of treatment. In some instances, hospitalization may be necessary, although the vast majority of patients respond to outpatient treatment.

Against this backdrop, it is noteworthy that in the TADS, 29% of the depressed young patients reported having clinically significant suicidal thoughts at baseline. At week twelve, the number of youth reporting any suicidal ideation had declined to 10%. Because youngsters who were most suicidal were excluded from the TADS sample, the proportion reporting suicidal thoughts when the study began was substantially lower than rates of suicidal ideation found in the community samples cited above (reference #3) of youth with major depressive disorder.

Without appropriate treatment, the consequences of depression are extremely serious. Four of ten youth will have a second episode of depression within two years. (Lewinsohn PM, et al.) They are also at increased risk for substance abuse, eating disorders, and adolescent pregnancy. (Kessler PC, et al.) Research indicates that over half of depressed youth will eventually attempt suicide, and an estimated 2- to 5% will die by suicide in the 10 to 20 years following an initial episode. (Fombonne et al).

What prompted the FDA warning in September of 2004?
In 2004, the FDA reviewed 23 clinical trials involving more than 4,300 child and adolescent patients who received any of nine different antidepressant medications. (Hammond). No suicides occurred in any of these studies. Most of the studies that the FDA examined used two measures to assess suicidal thinking and behavior.
1) All used "Adverse Event Reports," which are reports made by the research clinician if a patient (or their parent) spontaneously shares thoughts about suicide or describes potentially dangerous behavior. The FDA found that such "adverse events" were reported by approximately 4% of all children and adolescents taking medication compared with 2% of those taking a placebo. One of the problems with using this approach to measuring suicidal thinking is that most teenagers do not talk about their suicidal thoughts unless they are asked in which case no report is filed. (Gould MS, et al.)
2) In 17 of the 23 studies a second measure was also available. These were standardized forms asking about suicidal thoughts and behaviors completed for each child or teen at each visit. In the views of many experts these measures are more reliable than event

reports. The FDA's analysis of the data from these 17 studies found that medication neither increased suicidality that had been present before treatment, nor did it induce new suicidality in those who were not thinking about suicide at the start of the study. In fact, on these measures, all studies combined showed a slight reduction in suicidality over the course of treatment. Although the FDA reported both sets of findings, they did not comment on the contradiction between them.
Hence, the 2% and 4% spontaneous report rates need to be understood in the context of findings from community samples cited previously in which as many as half or more of teenagers with major depression are thinking about suicide at the time of diagnosis and some 16% to 35% have made a previous suicide attempt.

Although only nine medications were re-examined in the analysis, the FDA applied the labeling changes to all antidepressant medications. This was done on the basis of the advisory committee's perception that currently available data are inadequate to exclude any single medication from being potentially associated with the same increased risk for spontaneous reports of suicidal thinking and/or behavior found in the 23 studies.

Suicidality in adolescence
Suicidal ideation and suicide attempts are common in adolescence and do not have the same prognostic significance for completed suicide as those behaviors in later life.
The federal Centers for Disease Prevention and Control, or CDC, reports that 17% of adolescents think about suicide in a given year. (www.cdc.gov) Among high school students, 12% of girls and 5% of boys attempt suicide in a given year. Ultimately, 2 per 100,000 girls and 12 per 100,000 boys die as a result of such attempts — a ratio of attempts to completed suicide that is 6,000 to 1 among girls and 400 to 1 among boys. In the U.S., this translates into approximately 2000 young people who die each year as a result of suicide.
Fortunately, the overall rate of suicide in the 10-19 year age range has declined by 25% over the past decade. Since this decade has been associated with a dramatic increase in the prescription rates of the newer SSRI antidepressants, a recent study has demonstrated that a 1% increase in prescription of antidepressant medication was associated with a 0.23 per 100,000 decrease in adolescent suicides (Olfson, M. et al.)
It is important to consider clinical trial data in the context of these population-based data. In its review of 23 clinical trials involving child and adolescent subjects who received any of nine different antidepressant medications, the FDA combined the rates for suicidal thoughts and suicide attempts under the general term "suicidality." This has fostered a public impression that there is a high rate of suicide attempts or even completed suicides in children and adolescents that can be attributed to taking antidepressant medication; in fact, suicidal thoughts and actions decline with medication and psychotherapy treatments, and there were no completed suicides in the studies reviewed by FDA. Suicidal thoughts or attempts do not equal suicides.
Every suicide is a personal tragedy that may be linked to inadequate treatment monitoring or severe adverse side-effects of a medication. Yet the rise in overall population treatment rates with antidepressant medication has not been associated with a rise in completed suicides in the larger population — in fact, there has been a substantial decrease in completed suicides over the past decade. Likewise, the higher spontaneous reports of

suicidal ideation and attempts (referred to by the FDA as "adverse events") in children on antidepressants compared with placebo, has not been correlated with systematic assessments of suicidal ideation or attempts increasing with these medications. Research is needed to determine how the relatively low rate of spontaneous reports of adverse events is related to the much higher systematically assessed rates of suicidal ideation and attempts, and which more clearly indicate a risk for completed suicide.

In an illness where unwanted and spontaneous suicidal thoughts are integral symptom components, treatment that increases communication about these symptoms can lead to more appropriate monitoring and decreased risk for the adverse event of greatest concern — i.e. completed suicide.

Endnotes from ParentsMedGuide.org

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